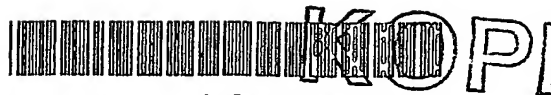




Europäisches Patentamt  
European Patent Office  
Office européen des brevets



Publication number: 0 575 841 A1

12

# EUROPEAN PATENT APPLICATION

21 Application number: 93109425.4

51 Int. Cl.<sup>5</sup>: A61K 31/00, A61K 31/47,  
A61K 31/56, A61K 31/60,  
A61K 33/06

22 Date of filing: 12.06.93

30 Priority: 16.06.92 JP 156961/92

43 Date of publication of application:  
29.12.93 Bulletin 93/52

84 Designated Contracting States:  
AT BE CH DE FR GB IT LI NL SE

71 Applicant: VITACAIN PHARMACEUTICAL CO.,  
Ltd.  
77, Hashibanishinocho 2-chome  
Moriguchi-shi, Osaka 570(JP)

72 Inventor: Hyodo, Masayoshi  
10-10, Kosobecho 4-chome  
Takatsuki-shi, Osaka 569(JP)  
Inventor: Akiyoshi, Masataka  
12-27, Isecho  
Ashiya-shi, Hyogo 659(JP)

74 Representative: von Kreisler, Alek,  
Dipl.-Chem. et al  
Patentanwälte  
von Kreisler-Selting-Werner  
Postfach 10 22 41  
D-50462 Köln (DE)

54 Composition containing dibucaine hydrochloride, a salicylate, calcium bromide and an antiphlogistic steroid for the treatment of pain.

57 A composition for treating pain, which contains dibucaine, a pharmaceutically acceptable salt of salicylic acid, calcium bromide, and antiphlogistic steroid(s) as active ingredients; and a method for reducing pain, which comprises injecting said composition into the location of pain. Further, the present invention provides a composition containing antiphlogistic steroid as an active ingredient, which is for reinforcing pain relief action of a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide; and a novel use of antiphlogistic steroid in the treatment of pain.

dibucain  
Ca-bromid  
Salicylsäure

EP 0 575 841 A1

## FIELD OF THE INVENTION

The present invention relates to injectable compositions for treating pain, methods for treating pain, and a novel use of antiphlogistic steroids.

## BACKGROUND OF THE INVENTION

Conventionally, pain caused by rheumatic diseases and locomotorium diseases has been treated with nonsteroidal antiinflammatory, local anesthetic and antispasmodic which are generally referred to as analgesics in a wide sense, and with vasoconstriction, vasodilator and muscular relaxant having other actions as well, which may be used in combination. This treatment using plural medicaments is based on the pain developing mechanisms, and the mechanism of action of medicaments. For example, a non-steroidal antiinflammatory exhibits etiotropic effects by inhibiting synthesis of the pain-producing substance prostaglandins, while a local anesthetic exhibits symptomatic effects by blocking transmission of neurostimulation from a local pain source to the center, and the combination of these medicaments aims at synergistic effects afforded by their different actions displayed at different sites. An exemplary of the medicaments formulated for achieving such synergistic effects is Neo Vitacain injection® (VITACAIN PHARMACEUTICAL CO., LTD., Japan), which is a local injection containing dibucaine hydrochloride, sodium salicylate, and calcium bromide as active ingredients and having a formulation shown below. This injection is markedly effective as an analgesic for use in a pain treatment of head neuralgia, muscle pain, rheumatism, low backache, etc. Usefulness of Neo Vitacain injection® and its analogous therapeutic compositions for the treatment of pain will be greatly enhanced if the effect thereof could be improved more.

Formulation of Neo Vitacain injection® (100 ml):

Dibucaine hydrochloride	100 mg
Sodium salicylate	300 mg
Calcium bromide	200 mg
Thiamine hydrochloride	200 mg
Pyridoxin hydrochloride	100 mg
Calcium pantothenate	100 mg

## SUMMARY OF THE INVENTION

An object of the present invention is to provide novel pharmaceutical compositions effective for algetic diseases.

Another object of the present invention is to provide methods for treating algetic diseases.

A still another object of the present invention is to provide a novel use of antiphlogistic steroids as contained in a composition for reinforcing pain relief action, which is used with other analgesic such as Neo Vitacain injection® for the treatment of pain.

The present inventors have conducted intensive studies with the aim of achieving the above-mentioned purposes, and found that a composition obtained by adding antiphlogistic steroid(s) to a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide has a pain relief effect which is superior to that of the conventional agents for treating pain, and that said composition is extremely useful for the treatment of pain. Moreover, the present inventors have found that the treatment using a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, calcium bromides and antiphlogistic steroid(s) is an extremely effective method for reducing pain. Still further, the present inventors have found that an antiphlogistic steroid can reinforce pain relief effect of a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide. With these findings, the present inventors have completed the present invention.

That is, the present invention is:

1. An injectable composition for treating pain, which contains dibucaine, a pharmaceutically acceptable salt of salicylic acid, calcium bromide, and antiphlogistic steroid(s);
2. A method for treating pain, comprising injecting a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, calcium bromide, and antiphlogistic steroid(s), into the location of pain;

3. A composition containing antiphlogistic steroid(s) and pharmaceutically acceptable carriers for reinforcing pain relief action of a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide; and

4. Use of antiphlogistic steroid(s) as contained in a composition for reinforcing pain relief action of a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide.

#### DETAILED DESCRIPTION OF THE INVENTION

The pain here particularly means pain at a local region or site, and includes myofascial pain, circumomarthrits, symptomatic neuralgia, and transdermal, muscular and articular pain accompanying locomotorium diseases. Specific examples include occipital neuralgia, temporal neuralgia, muscle pain, neuralgia, chronic rheumatism, low backache, backache, pain caused by autonomic nerve sensitivity, migraine, trigeminal pain, frozen shoulder, and pain caused by disorders of autonomic nerve (e.g. algetic insomnia, menopausal neuralgia).

The treatment of pain in this specification means treatments given for the purpose of removing or alleviating the above-mentioned pains.

The dibucaine to be used in the present invention is normally in the form of a salt, with preference given to dibucaine hydrochloride.

The antiphlogistic steroid to be used in the pharmaceutical composition of the present invention may be any antiphlogistic steroid as long as it can be used as an injection, and examples thereof include dexamethasone, betamethasone, methylprednisolone, prednisolone, and salts thereof. These antiphlogistic steroids are normally used in the form of pharmaceutically acceptable salts, and are exemplified by dexamethasone acetate, dexamethasone palmitate, dexamethasone sodium phosphate, dexamethasone sodium metasulfobenzoate, betamethasone acetate, betamethasone sodium phosphate, prednisolone acetate, prednisolone butylacetate, prednisolone sodium succinate, methylprednisolone acetate and methylprednisolone sodium succinate, with preference given to dexamethasone sodium phosphate, betamethasone sodium phosphate, and methylprednisolone acetate.

The pharmaceutically acceptable salt of salicylic acid to be used in the present invention is exemplified by alkali metal salts, and preferred is sodium salt.

The composition for treating pain of the present invention contains each component at a proportion of 100-1000 parts by weight, preferably 200-500 parts by weight of a pharmaceutically acceptable salt of salicylic acid, and 50-500 parts by weight, preferably 100-300 parts by weight of calcium bromide per 100 parts by weight of dibucaine. The proportion of the antiphlogistic steroid varies depending on the kind thereof, and dexamethasone and betamethasone are normally contained in a proportion of 4-80 parts by weight, preferably 6-40 parts by weight, and prednisolone and methylprednisolone are normally contained in a proportion of 80-2000 parts by weight, preferably 100-1000 parts by weight per 100 parts by weight of dibucaine.

In Table 1, the amounts of various antiphlogistic steroids to be added to 5 ml of, for example, Neo Vitacain injection® are detailedly shown. The amounts shown here are on an antiphlogistic steroid basis, and in practice, they are recalculated into the salt amounts to be preferably used.

Table 1

Amounts of various steroids to be added to 5 ml of Neo Vitacain		
Steroid to be added	normal amount (mg)	preferable amount (mg)
Dexamethasone	0.2 - 4.0	0.3 - 2.0
Betamethasone	0.2 - 4.0	0.3 - 2.0
Methylprednisolone	4.0 - 80.0	5.0 - 40.0
Prednisolone	5.0 - 100.0	5.0 - 50.0

The composition of the present invention may contain additives normally accepted from the aspect of the formulation of pharmaceutical preparations. For example, carriers, stabilizers (e.g. creatinine), solubilizers (e.g. glycerin), suspending agents (e.g. carboxymethylcellulose), buffers (e.g. citric acid, sodium hydrogencarbonate), emulsifiers (e.g. fatty acid monoglyceride, sorbitan fatty acid ester, polyoxyethylene lauryl ether, etc.), antiseptics (e.g. methyl p-oxybenzoate, propyl p-oxybenzoate, etc.) and antioxidants (e.g.

t-butyl-hydroxyanisole) may be added to liquid compositions, and excipients may be further added to powder compositions.

In the present invention, the aforementioned compositions are preferably injected into the location site of pain, and for this reason, the compositions of the present invention for the treatment of pain may take any form as long as they can be prepared into injections when in use. Examples thereof include aqueous solution, suspension, emulsion, and powders to be dissolved, suspended or emulsified when in use. They may be prepared by conventional methods. The pH of the aqueous solution, suspension, and emulsion is preferably within the range of from pH 4 to 7, particularly preferably at about pH 6, in which a long-term storage can be attained despite the instability of dexamethasone phosphate in the acidic range and instability of dibucaine hydrochloride in the alkali range, and pH of the preparations is adjusted to said range by conventional methods. Also, the powder compositions may be prepared in such a manner as adjusts their pH to be in the range of from 4 to 7, preferably about 6 upon dissolution in sterilized water or sterilized physiological saline.

The composition for the treatment of pain, and the composition for reinforcing pain relief action of the present invention are administered to mammals such as human, dog, cow, horse and cat, particularly to human.

The composition for treating pain and composition for reinforcing pain relief action of the present invention are injected locally, such as into muscle, peritendon and articular cavity.

While the dose of the composition for treating pain of the present invention varies depending on age of patients, symptom, administration site and drugs to be used, taking a therapeutic composition of the above-described formulation wherein antiphlogistic steroid(s) is(are) added to 5 ml of Neo Vitacain injection® in an amount given in Table 1, as an example, it is normally 0.1-25 ml, preferably 0.5-5 ml per site, namely, 0.1-25 mg, preferably 0.5-5 mg of dibucaine hydrochloride, 0.1-250 mg, preferably 1-25 mg of sodium salicylate, 0.05-125 mg, preferably 0.5-15 mg of calcium bromide, to which 0.004-500 mg of antiphlogistic steroid(s) may be added, wherein 0.004-20 mg, preferably 0.03-2 mg of dexamethasone and/or betamethasone, and/or 0.08-500 mg, preferably 0.5-50 mg of methylprednisolone and/or prednisolone is(are) used as the antiphlogistic steroid(s).

Since the method for treating pain of the present invention permits long-lasting and potent pain treating effects, intermittent administration can be performed. While administration frequency differs depending on age of patients, symptom and pain location, administration of once or twice a week, or 1 to 4 times in 2 weeks can exert sufficient effects. The method for treating pain of the present invention affords not only superior pain relief effect but also reduced pain at the time of the needle puncture and insertion of a drug.

In the present invention, the composition for reinforcing pain relief action is a general concept embracing those having an action of potentiating pain relief action when added to a compound or composition having pain relief action or when used independently but together with said compound or composition. In the present invention, it means a composition containing, as an active ingredient, antiphlogistic steroid which is capable of additionally reinforcing pain reducing effect possessed by a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid and calcium bromide, when added thereto or used independently but together with said composition.

The composition for reinforcing pain relief action of the present invention may be in the form of injectable solutions, suspensions or emulsions, or powders which can be dissolved, suspended or emulsified when in use as an injection.

The aforementioned additives for the composition for treating pain may be also added to the composition for reinforcing pain relief action.

The use of the composition for reinforcing pain relief action may be performed by adding same to an injectable composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide, particularly Neo Vitacain injection®, or by an independent use thereof together with a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide when it is used for the treatment of pain.

The composition for reinforcing pain relief action of the present invention is preferably used in admixture with an injectable composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide. The composition for reinforcing pain relief action is added to said composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide in the same amount as that in the aforementioned composition for treating pain, on an antiphlogistic steroid basis. That is, the composition for reinforcing pain relief action is added in an amount of 0.25-800 parts by weight per 100 parts by weight of the total amount of dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide, on an antiphlogistic steroid basis.

Each component and the composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide to be used in the present invention have been conventionally used as pharmaceuticals, and safety thereof in the above-mentioned administration amounts has been already established. For example, acute toxicity of Neo Vitacain injection® is as shown in LD<sub>50</sub> of 34 ml/kg, and addition thereto or independent use together therewith of antiphlogistic steroid in an amount mentioned above did not result in significant increase of toxicity.

Example 1 (Injection formulation, 100 ml)	
Dibucaine hydrochloride	100 mg
Sodium salicylate	300 mg
Calcium bromide	200 mg
Thiamine hydrochloride	200 mg
Pyridoxin hydrochloride	100 mg
Calcium pantothenate	100 mg
Dexamethasone sodium phosphate	20 mg

Example 2 (Injection formulation, 100 ml)	
Dibucaine hydrochloride	100 mg
Sodium salicylate	300 mg
Calcium bromide	200 mg
Betamethasone sodium phosphate	20 mg

Example 3 (Injection formulation, 100 ml)	
Betamethasone sodium phosphate	200 mg
Sodium sulphite	30 mg
p-Oxybenzoic acid	75 mg
Creatinine	400 mg

Example 4 (Composition for reinforcing pain relief action, Injection formulation, 100 ml)	
Methylprednisolone acetate	2 g
Polyethylene glycol	3 g

The pain relief action of the composition for treating pain of the present invention, and the reinforcing effect of the composition for reinforcing pain relief action of the present invention on the agents for treating pain are hereinbelow described in detail.

#### Experiment 1

To a patient (male, age 63) who had been suffering from myofascial low backache for 2 months was administered the following medicament once a week, and the degree of pain before administration every week was compared.

In evaluating the pain, the initial pain was taken as 10, and the absence of pain was taken as 0, which is the same in the following experiments.

#### Medicament administered

- A : Neo Vitacain 3 ml  
B : Neo Vitacain 3 ml + Dexamethasone sodium phosphate 0.5 mg

Administration site

Medicament A : left lumbar region

Medicament B : right lumbar region

The results are summarized in Table 2, in which it is shown that addition of an antiphlogistic steroid to Neo Vitacain resulted in earlier removal of the pain than the sole use of Neo Vitacain, thereby indicating remarkable potentiation of the effect of pain treatment.

Table 2

	before 1st administration	before 2nd administration	before 3rd administration	before 4th administration	before 5th administration
Neo Vitacain	10	6	4	3	1
Neo Vitacain + steroid	10	4	0	-	-

## Experiment 2

To a patient (female, age 27) who had been suffering from tenosynovitis of both thumbs for 3 months was administered the following medicament once a week, and the effect was evaluated as in Experiment 1.

Medicament administered

A : Neo Vitacain 0.5 ml

B : Neo Vitacain 0.5 ml + Dexamethasone sodium phosphate 0.1 mg

Administration site

Medicament A : right thumb

Medicament B : left thumb

The results are summarized in Table 3, in which it is shown that addition of an antiphlogistic steroid to Neo Vitacain resulted in earlier removal of the pain than the sole use of Neo Vitacain, thereby indicating remarkable potentiation of the effect of pain treatment.

Table 3

	before 1st administration	before 2nd administration	before 3rd administration	before 4th administration
Neo Vitacain	10	7	5	3
Neo Vitacain + steroid	10	3	0	-

## Experiment 3

To a patient (male, age 46) who had been suffering from myofascial pain (*tenchu* syndrome) at the nuchal region for 1 month was administered the following medicament particularly at the *tenchu* part of the right and left nuchal regions, and the effects were evaluated as in Example 1.

Medicament administered

A : Neo Vitacain 2 ml

B : Neo Vitacain 2 ml + Methylprednisolone acetate 4 mg

Administration site

Medicament A : left nuchal region

Medicament B : right nuchal region

- 5 The results are summarized in Table 4, in which it is shown that addition of an antiphlogistic steroid to Neo Vitacain resulted in earlier removal of the pain than the sole use of Neo Vitacain, thereby indicating remarkable potentiation of the effect of pain treatment.

Table 4

10

	before 1st administration	before 2nd administration	before 3rd administration	before 4th administration	before 5th administration
Neo Vitacain	10	7	5	4	4
15 Neo Vitacain + steroid	10	4	2	2	0

Claims

- 20 1. An injectable composition for treating pain, which contains dibucaine, a pharmaceutically acceptable salt of salicylic acid, calcium bromide and antiphlogistic steroid(s).
2. A composition for treating pain according to Claim 1, which is a liquid having a pH in the range of from 4 to 7.
- 25 3. A composition for treating pain according to Claim 1 or Claim 2, which contains 100 parts by weight of dibucaine, 100-1000 parts by weight of a pharmaceutically acceptable salt of salicylic acid, 50-500 parts by weight of calcium bromide, and 4-2000 parts by weight of antiphlogistic steroid(s).
- 30 4. A composition for treating pain according to Claim 1, which contains 0.1-25 mg of dibucaine hydrochloride, 0.1-250 mg of a pharmaceutically acceptable salt of salicylic acid, 0.05-125 mg of calcium bromide, and 0.004-500 mg of antiphlogistic steroid(s) per administration at one site.
- 35 5. A composition for treating pain according to any one of Claims 1 to 4, wherein the antiphlogistic steroid is at least one member selected from the group consisting of dexamethasone, betamethasone, methylprednisolone, prednisolone and their pharmaceutically acceptable salts.
- 40 6. A method for treating pain, characterized by injecting a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, calcium bromide, and antiphlogistic steroid(s) into the location of pain.
- 45 7. A method for treating pain according to Claim 6, wherein the composition contains each component in a proportion of 100 parts by weight of dibucaine, 100-1000 parts by weight of a pharmaceutically acceptable salt of salicylic acid, 50-500 parts by weight of calcium bromide, and 4-2000 parts by weight of antiphlogistic steroid(s).
- 50 8. A method for treating pain according to Claim 6 or Claim 7, wherein the composition is a liquid having a pH in the range of from 4 to 7.
9. A method for treating pain according to Claim 6, wherein the administration is conducted once or twice a week.
10. A method for treating pain according to Claim 6, wherein administration is conducted 1 to 4 times in 2 weeks.
- 55 11. A method for treating pain according to Claim 9 or Claim 10, which comprises administration of a composition containing 0.1-25 mg of dibucaine hydrochloride, 0.1-250 mg of a pharmaceutically acceptable salt of salicylic acid, 0.05-125 mg of calcium bromide, and 0.004-500 mg of antiphlogistic

steroid(s) per administration at one site.

- 5 12. A composition for reinforcing pain relief action of a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide, which contains antiphlogistic steroid as an active ingredient.
- 10 13. A composition according to Claim 12, which is for reinforcing pain relief action of a composition containing 100 parts by weight of dibucaine, 100-1000 parts by weight of a pharmaceutically acceptable salt of salicylic acid, and 50-500 parts by weight of calcium bromide.
- 15 14. A composition for reinforcing pain relief action according to Claim 12 or Claim 13, wherein the antiphlogistic steroid is at least one member selected from the group consisting of dexamethasone, betamethasone, methylprednisolone, prednisolone and their pharmaceutically acceptable salts.
- 20 15. Use of a composition containing antiphlogistic steroid as an active ingredient, for reinforcing pain relief action of a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide in the treatment of pain.
- 25 16. Use of a composition for reinforcing pain relief action according to Claim 15, characterized by adding, when in use, antiphlogistic steroid to an injectable composition for treating pain containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide.
- 30 17. Use of a composition for reinforcing pain relief action according to Claim 15, wherein a composition containing antiphlogistic steroid as an active ingredient is administered independently but together with a composition containing dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide, in the treatment of pain.
- 35 18. Use of a composition for reinforcing pain relief action according to any one of Claims 15 to 17, wherein the antiphlogistic steroid is at least one member selected from the group consisting of dexamethasone, betamethasone, methylprednisolone, prednisolone and their pharmaceutically acceptable salts.
- 40 19. Use of a composition for reinforcing pain relief action according to any one of Claims 15 to 17, wherein the antiphlogistic steroid is contained, as an active ingredient, in a proportion of 0.25-800 parts by weight per 100 parts by weight of the total amount of dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide.
- 45 20. Use of a composition for reinforcing pain relief action according to Claim 18, wherein the antiphlogistic steroid is contained, as an active ingredient, in a proportion of 0.25-800 parts by weight per 100 parts by weight of the total amount of dibucaine, a pharmaceutically acceptable salt of salicylic acid, and calcium bromide.





European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 93 10 9425

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CLS)
Y	PHARMACOMETRICS (JAPAN) vol. 20, no. 4, 1980, pages 693 - 701 TSUTOMU KAMEYAMA ET AL. 'Dibucaine hydrochloride, sodium salixylate and calcium bromide' * abstract *	1-20	A61K31/00 A61K31/47 A61K31/56 A61K31/60 A61K33/06
Y	J. INDIAN MED. ASSOC vol. 82, no. 11, 1984, pages 397 - 399 SAMIR K. GUPTA ET AL. 'Tietze's Syndrome' * page 399, left column, paragraph 5 - right column, paragraph 1 *	1-20	
			TECHNICAL FIELDS SEARCHED (Int. CLS)
			A61K
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 27 SEPTEMBER 1993	Examiner TZSCHOPPE D. A.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure F : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application I : document cited for other reasons * : member of the same patent family, corresponding document	